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PCT/EP2003/003973

Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference A2002/00656	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP2003/003973	International filing date (*day/month/year*) 16 April 2003 (16.04.2003)	Priority date (*day/month/year*) 29 April 2002 (29.04.2002)
International Patent Classification (IPC) or national classification and IPC A61K 9/127, 9/16, 31/355, 31/015		
Applicant BIOTESYS GMBH		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand 13 November 2003 (13.11.2003)	Date of completion of this report 24 September 2004 (24.09.04)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/EP2003/003973

I. Basis of the report

1. With regard to the elements of the international application:*

☐ the international application as originally filed

☒ the description:

pages 1-16, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

☒ the claims:

pages _____, as originally filed

pages _____, as amended (together with any statement under Article 19

pages _____, filed with the demand

pages 1-23, filed with the letter of 13 May 2004 (13.05.04)

☒ the drawings:

pages 1/2-2/2, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

☐ the sequence listing part of the description:

pages _____, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☒ contained in the international application in written form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/fig _____

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

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III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 3

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 3 are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/EP 03/03973

I. Basis of the report

1. This report has been drawn on the basis of *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

5.

The new set of claims submitted with the fax of 13 May 2004 fails to meet the requirements of PCT Article 19(2) because the content of claim 1 goes beyond the disclosure in the international application as filed. The term "substance" is broader than the original term "active substance". Furthermore, a basis for the use of the term "liposome" could not be found.

For these reasons, this report has been established without taking the submitted amendments into account.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: III.1

The phrase "chemically inert substance such as, for example, nanoparticles such as carbon nanotubes, nanothreads, colloids, etc." used in claim 3 is unclear and leaves the reader uncertain as to the meaning of the technical features involved. Consequently, the definition of the subject matter of this claim is not clear (PCT Article 6).

Furthermore, is not clear whether conjunction between "amino acids" and "chemically inert substance" should be "and" or "or".

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V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	9, 11, 14-19, 22	YES
	Claims	1-2, 4-8, 10, 12-13, 20-21, 23-24	NO
Inventive step (IS)	Claims	11	YES
	Claims	9, 14-19, 22	NO
Industrial applicability (IA)	Claims	1-2, 4-24	YES
	Claims		NO

2. Citations and explanations

The prior art documents are numbered according to their order in the research report.

1) Novelty

The content of claims 1, 2, 4-8, 10, 12-13, 20-21 and 23-24 is not novel within the meaning of PCT Article 33(2).

D1 describes a selective transport system consisting of liposomes, peptides being coupled to the phospholipid layer of said liposomes via a polyethylene oxide spacer (see abstract, figure 2 and page 242, column 1, second paragraph). The modified liposomes are used for the selective transport of an active substance to particular cells of the organism (see page 245, column 1, second and third paragraphs). The docking of the liposome modified with a linear RGD peptide to integrin GPIIb-IIIa is selected as a model example of selective transport (see abstract). The RGD peptide with the sequence GSSSGRGDSPA comprises sequence ID NO: 1 specified in claim 8, the sequence section Arg-Gly-Asp (= RGD) being responsible for the bond to the integrin (see page 240, column 1, third paragraph).

D2 describes active substance-containing phospholipid liposomes whose surfaces are occupied by ligands that bind

to specific cells (see claims 23-43). Sterile barriers are used as spacers between the liposome and ligand (see claims 42-43). Liposomes modified in this manner are suitable as transport systems for active substances such as anti-tumor agents, anesthetics, beta-blockers, antibiotics, antidepressants, vitamins, enzymes or immunostimulating agents (see page 30, line 20 to page 31, line 32). These liposomes can generally be loaded with any product (see page 32, line 20-23).
The content of claims 1-2, 4-8, 10, 12-13, 20-21 and 23-24 is therefore not novel.

2) Inventive step
The content of claims 9, 14-19 and 22 does not involve an inventive step within the meaning of PCT Article 33(3).
The problem addressed by the present application is that of providing a better system for the target-oriented biological transport of active substances.
The solution is a liposome with attached oligopeptides whose sequences are binding sites for proteins.
Since in D1, peptides with the RGD sequence have already been used successfully with liposomes for specifically binding to integrin GPIIb-IIIa, and thus for the targeted use of anticoagulants, a person skilled in the art can directly and clearly deduce that liposomes that are derived with specific peptide sequences for binding to retinal cells can be used for the target-controlled transport of active substances to the retina. The sequences 9 to 15 disclosed in the present application are subsequences of R-cadherin (see **D4**), which is a protein for cell-to-cell adhesion for the retina. It is therefore obvious for a person skilled in the art to couple this peptide to the liposome for targeted administration to the retina.

Since D1 clearly states that any active substance can be administered via modified liposomes, the administration of micronutrients such as vitamins or trace elements via modified liposomes does not involve an inventive step because a surprising and unexpected effect is not discernible.
The content of claims 9, 14-19 and 22 is therefore not inventive.

3) Industrial applicability

The content of claims 1-2 and 4-24 is industrially applicable within the meaning of PCT Article 33(4).